CURRENT ONCOLOGY
A Canadian Cancer Research Journal

SHORT COMMUNICATION

Management of chronic lymphocytic leukemia in Canada during the coronavirus pandemic

L.H. Sehn MD,* P. Kuruvilla MD,† A. Christofides MSc RD,‡ and J. Stakiw MD§

ABSTRACT

The emergence of the COVID-19 disease pandemic caused by the 2019 novel coronavirus has required a re-evaluation of treatment practices for clinicians caring for patients with chronic lymphocytic leukemia (CLL). The American Society for Hematology (ASH) has provided a series of recommendations for the treatment of patients with CLL during the pandemic, covering a range of topics, including testing for COVID-19, CLL treatment initiation and selection, use of immunoglobulin therapy, in-person monitoring, and treatment of patients with CLL and COVID-19. We summarize the ASH recommendations and discuss their applicability as guidelines for the treatment of CLL during the COVID-19 pandemic in Canada.

Key Words Coronavirus, COVID-19, chronic lymphocytic leukemia

Curr Oncol. 2020 June:27(3)e332–e335 www.current-oncology.com

BACKGROUND

Patients with chronic lymphocytic leukemia (CLL) present a unique set of challenges for treating clinicians. Infection is a frequent cause of morbidity and mortality, occurring in approximately 70% of patients, with about 30% being categorized as major infections (defined as requiring hospital admission or intravenous antimicrobial treatment)[1]. Moreover, mortality rates of about 40% are reported to be directly attributable to those infections[2–4]. With a median age at diagnosis of 72 years in Canada, many patients are elderly and have comorbidities that further increase the morbidity and mortality associated with acquired infections[5,6].

Coronaviruses are a family of viruses that can cause illnesses such as the common cold, severe acute respiratory syndrome, and Middle East respiratory syndrome[7]. In 2019, a new coronavirus was identified as the cause of a disease outbreak that originated in China. The virus is known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing a disease called coronavirus disease 2019 (COVID-19)[7]. In March 2020, the World Health Organization declared the COVID-19 outbreak a pandemic[7].

Currently, a disproportionately higher incidence of severe COVID-19 has not been reported in patients with CLL compared with patients having other malignancies[8]. However, given the increased risk of infection in the CLL population and the associated morbidity and mortality, it is important to ensure that patients with CLL are protected, while still being optimally treated during the COVID-19 outbreak.

The American Society for Hematology (ASH) has provided a series of recommendations for the treatment of patients with CLL (with or without the COVID-19 infection) during the time of the pandemic, which are available at https://www.hematology.org/covid-19/covid-19-and-cll ("COVID-19 and CLL: Frequently Asked Questions")[8]. Similar guidelines have also been provided by ASH for indolent and mantle cell lymphomas, and for other hematologic malignancies (see https://www.hematology.org/covid-19#faq). The ASH recommendations are also referenced by the European Hematology Association. In addition, guidelines for radiation therapy of hematologic malignancies during the COVID-19 pandemic have been published by the International Lymphoma Radiation Oncology Group to address potential limitations of treatment resources and the need to reduce exposure of patients and staff to the potential for infection with COVID-19[5,9]. Although radiation therapy is of limited utility in the treatment of CLL, judicious use of radiation can delay the need for systemic therapy, particularly in patients with small lymphocytic lymphoma

Correspondence to: Laurie Sehn, Division of Medical Oncology, University of British Columbia, Vancouver, British Columbia V6T 1Z4
E-mail: Lsehn@bccancer.bc.ca ■ **DOI:** https://doi.org/10.3747/co.27.6769

and other lymphoma subtypes. In the present paper, we summarize the ASH recommendations and discuss their applicability as guidelines for the treatment of CLL during COVID-19 in Canada.

APPLICABILITY OF ASH RECOMMENDATIONS FOR CANADA

Testing for COVID-19

ASH Recommendations

- Testing for SARS-CoV-2 in mildly symptomatic patients with CLL depends on the accessibility of testing, the availability of treatment for COVID or other infections, and the need to isolate a COVID-positive patient from others.
- Unless the patient happens to already be in clinic, some test only patients whose symptoms warrant medical intervention, primarily because of limited test availability and the risk of spreading disease by bringing the patient into clinic.
- Others test aggressively for SARS-CoV-2 and other respiratory viruses despite mild symptoms because of the risk of other pathogens and the desire to isolate anyone with a communicable respiratory virus.
- All patients with more severe symptoms should be tested.

Canadian Perspective

Currently, patients with symptoms suspicious for COVID-19 are being tested, particularly those with symptoms of modest or greater severity. In addition, some centres are testing patients before the start of systemic therapy, even if the patients are asymptomatic. There is also a movement to test patients from areas with COVID-19 community outbreaks.

In general, the threshold for testing should be lower in patients with cancer (including CLL) than in the general population, given higher vulnerability in the cancer population. Clinicians should also be allowed to test patients based on their clinical judgment.

Factors affecting the decision to test include accessibility of testing, availability of treatment for COVID-19 or other infections, and the need to isolate a patient positive for COVID-19 from others. As testing becomes more readily available, the threshold for testing should be further lowered. Moreover, once testing for COVID-19 immunity is readily available, testing of patients with CLL could be valuable to enable assessment of future risk.

Treatment Initiation

ASH Recommendations

- It is our practice to postpone treatment initiation if possible.

Canadian Perspective

For noncurative therapy, delay of treatment initiation during the COVID-19 crisis is preferable, provided patients can be safely monitored for disease progression. However, treatment for those patients should not be delayed for long, and delay is reasonable only in patients who are borderline for therapy and can be carefully monitored to avoid progression to more advanced disease (such as development of bulky adenopathy or cytopenias).

Treatment Selection

ASH Recommendations

- For patients who require immediate therapy, we still offer the best treatment option considering disease- and patient-specific factors.
- When more than one option is a possibility, preference should be given to treatments that can be provided in the outpatient setting and that require fewer clinic visits and lab assessments.
- We try to avoid or skip treatment with monoclonal antibodies (MAbs: rituximab, obinutuzumab), especially when given in combination with targeted agents.
- Initiation of venetoclax requires multiple and extended clinic visits, with lab testing. If possible, venetoclax initiation should be avoided unless considered the most appropriate treatment for a particular patient.

Canadian Perspective

Most patients who require initiation of therapy are receiving a Bruton tyrosine kinase inhibitor (for example, ibrutinib), because that therapeutic class has the most favourable risk–benefit ratio for use during the pandemic. Depending on the prevalence of COVID-19 in the community, a Bruton tyrosine kinase inhibitor would be preferred over fludarabine–cyclophosphamide–rituximab even for young, fit patients with immunoglobulin heavy chain variable mutations.

In general, clinicians should balance treatment efficacy and toxicity with the additional risks created by the COVID-19 pandemic. Ideally, where treatments are equally effective, those with the least toxicity should be selected to avoid infectious complications. Treatments that minimize COVID-19 exposure risk for both patients and staff, such as oral rather than intravenous therapies, are preferred. Moreover, therapies that do not require frequent laboratory tests, on-site visits, or the need for hospitalization are preferred. If a part of standard therapy, with proven value, MAbs should not be eliminated. However, treatment with MAbs will add to immunosuppression and will require on-site visits; alternatives should be selected if equally effective and available.

Intravenous Immunoglobulin Therapy

ASH Recommendations

- In patients without COVID-19, we continue intravenous immunoglobulin (IVIG) treatments only for highly selected patients with a history of hypogammaglobulinemia and active or recurrent severe infections, for whom the potential benefits are outweighed by the risks of coming to clinic for the infusion. Even in those cases, less frequent infusions should be considered when possible (for example, every 6–8 weeks) targeting an immunoglobulin G level of 400–500 mg/dL.
- In patients with CLL and COVID-19, IVIG can be continued. Given the higher risk of thromboembolic

events with COVID-19, we recommend assessment of risks versus benefits in each patient and close monitoring for thromboembolic symptoms.

Canadian Perspective

Typically, immunoglobulin therapy is used judiciously for patients with hypogammaglobulinemia and recurrent, severe infections. For patients without strong indications for IVIG, it might be prudent to avoid or discontinue treatment to minimize the frequency of visits. For patients with CLL and COVID-19, IVIG infusions can be held until the patient recovers, unless IVIG is felt to be beneficial for management of the virus. At many cancer centres, patients are treated with subcutaneous rather than intravenous immunoglobulin. Because subcutaneous immunoglobulin can be self-administered at home, it should, where possible, be used in preference to the intravenous formulation during the pandemic.

In-Person Monitoring

ASH Recommendations

- When possible, we try to minimize the number of visits for patients who are stable and doing well.
- When follow-up is necessary, using laboratories closer to home and using telemedicine are recommended.
- Most continue ongoing CLL-directed therapies in unaffected patients; exceptions are monoclonal anti-CD20 antibodies and IVIG.

Canadian Perspective

Attempts should be made to minimize imaging and bloodwork monitoring to limit the potential for COVID-19 exposure. Whenever possible, appointments should be conducted virtually, and bloodwork should be obtained from local laboratories. The need to diminish the exposure risk could be even more important in localities with a greater prevalence of COVID-19 or in rural settings where access to tertiary-level care in the event of severe respiratory distress is limited. For patients taking oral therapies, it might be preferable to dispense medications for up to 12 weeks at a time and to have the pharmacy mail the drug when appropriate. Although ASH suggests holding MAbs, it is reasonable to continue MAbs if they have proven value within the regimen being used. Similarly, immunoglobulin treatment should be given if there is a valid indication to begin or continue treatment.

Patients with COVID-19

ASH Recommendations

- For outpatients with mild symptoms, we don't modify therapy.
- A decision about treatment modification in patients with more severe symptoms depends on weighing the aggressiveness of the CLL and a history of frequent infections against the theoretical risk of more severe COVID complications.
- Currently, there is not enough evidence to suggest that the approach should be different for specific classes of targeted CLL drugs. Decisions to hold or continue treatments are made on a case-by-case basis.
- There is general agreement on holding MAbs for COVID-positive patients.
- If the patient is receiving a B cell receptor signalling inhibitor (ibrutinib, acalabrutinib, idelalisib, duvelisib), discontinuation can sometimes result in CLL flare and cytokine release that can mimic some of the symptoms of COVID-19. Resumption of the B cell receptor signalling inhibitor generally results in resolution of the symptoms in a relatively short period of time.

Canadian Perspective

In the case of a patient with COVID-19, few data are available to guide the concurrent management of CLL. Decisions should be made on a patient-by-patient basis and should consider disease risk, patient comorbidities, toxicity of treatment in current use, and the severity of the COVID-19 symptoms. Clinicians might elect to proceed with treatment or to hold therapy for 2–3 weeks until the infection has cleared. Patients with the poorest fitness level will be the most vulnerable to the complications of COVID-19, and treatment should therefore be very conservative.

Few data are available to guide the continuation or holding of individual classes of agents in patients with COVID-19. Physicians will have to rely on clinical judgment. In patients receiving B cell receptor signalling inhibitors, abrupt discontinuation can occasionally result in flare of CLL. Interestingly, a recent report of a small case series of patients with Waldenström macroglobulinemia suggested that the Bruton tyrosine kinase inhibitor ibrutinib could be safely continued in patients with active COVID-19, and postulated that ibrutinib might have protective effects against lung injury[10]. However, it should be acknowledged that the safety and efficacy of ibrutinib in the setting of COVID-19 and ibrutinib's effect on respiratory disease have not been established and require further evaluation. As discussed earlier, MAbs could be continued when felt to be beneficial to the treatment regimen.

SUMMARY

The ASH recommendations for the treatment of patients with CLL during the COVID-19 pandemic are a valuable tool for clinicians and are largely applicable to Canada. As the understanding of COVID-19 increases and as testing and treatments improve, treatment of patients with CLL and other malignancies will likely evolve.

The ASH Research Collaborative's Data Hub has established a COVID-19 registry for patients with hematologic malignancies. This new resource provides near real-time clinical data summaries about patients with COVID-19 who have a history of hematologic malignancy. All treating clinicians are urged to contribute to the registry: collecting and learning from current experience will help to prepare for future events. The registry can be accessed at https://www.ashresearchcollaborative.org/covid-19-registry. With a careful approach, it is hoped that patients with CLL can continue to be optimally treated for their disease while minimizing their risk of viral exposure and infection.

ACKNOWLEDGMENTS

The authors acknowledge support from Janssen Canada Inc. for the development of this article. Medical writing and editorial

assistance were provided by, respectively, Anna Christofides and Sarah Doucette of IMPACT Medicom Inc.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: Medical writing support provided by AC of IMPACT Medicom Inc. was funded by Janssen Canada. LS has received honoraria from Hoffmann–La Roche/Genentech, AbbVie, Amgen, Apobiologix, AstraZeneca, Celgene, Gilead, Janssen, Kite, Karyopharm, Lundbeck, Merck, MorphoSys, Seattle Genetics, Teva Pharmaceuticals, Takeda, and Verastem Oncology. PK has received conference support and speaker fees from Janssen, AstraZeneca, and AbbVie. JS has received honoraria for speaking engagements and consultancy meetings from Janssen, Celgene, AbbVie, AstraZeneca, Roche, Apobiologix, and GlaxoSmithKline.

AUTHOR AFFILIATIONS

*BC Cancer, Centre for Lymphoid Cancer, and University of British Columbia, Vancouver, BC; †William Osler Health System, Brampton Civic Hospital, Brampton, ON; ‡IMPACT Medicom Inc., Toronto, ON; §Saskatoon Cancer Centre, Saskatchewan Cancer Agency, Saskatoon, SK.

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